

(CAM) refers to products and regimens that individuals may employ either to enhance wellness, relieve symptoms of disease and side effects of conventional treatments, or cure disease. CAM articles provide evidence-based information on promising complementary and alternative methods, and inform clinicians of methods that may harm patients.

Integrative Oncology: Complementary Therapies for Pain, Anxiety, and Mood Disturbance

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ABSTRACT Many people with cancer experience pain, anxiety, and mood disturbance. Conventional treatments do not always satisfactorily relieve these symptoms, and some patients may not be able to tolerate their side effects. Complementary therapies such as acupuncture, mind-body techniques, massage, and other methods can help relieve symptoms and improve physical and mental well-being. Self-hypnosis and relaxation techniques help reduce procedural pain. Acupuncture is well documented to relieve chronic cancer pain. Massage and meditation improve anxiety and other symptoms of distress. Many dietary supplements contain biologically active constituents with effects on mood. However, not all complementary therapies are appropriate or useful, and even helpful complementary modalities may not be optimal under some circumstances. Situations when precaution is indicated include acute onset of symptoms and severe symptoms, which require immediate mainstream intervention. Dietary supplements are associated with serious negative consequences under some circumstances. The authors summarize the research on these modalities and discuss the rationale, expectation, and necessary precautions involved with combining complementary therapies and mainstream care. Practical clinical issues are addressed. (*CA Cancer J Clin* 2005;55:109–116.) © American Cancer Society, Inc., 2005.

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INTRODUCTION

People with cancer commonly experience a range of symptoms, including pain and various types of physical and emotional distress. These symptoms span the course of the disease. Immediately after diagnosis, anxiety and other mood disturbances may occur, and these can fluctuate over time in response to remission, recurrence, and the diagnosis of refractory disease. During treatment, nausea, vomiting, and procedure-related pain and distress are encountered. Pain, distress, and depression are important target symptoms in end-stage patients under palliative care.

Conventional treatments do not always satisfactorily relieve these symptoms, and some patients may not be able to tolerate their side effects. Complementary therapies such as acupuncture, mind-body techniques, massage, and other methods can relieve symptoms and improve physical and emotional well-being when used in conjunction with mainstream care. An important distinction must be made between complementary therapies and “alternative therapies,” which are unproven methods typically promoted for use instead of conventional cancer treatment. They can be harmful and often are bogus.¹

By combining the best of complementary modalities with mainstream conventional therapies, we can practice “integrative medicine.” Here we discuss how clinicians can integrate conventional and complementary therapies most effectively into the overall strategy of symptom control in patients with cancer (Table 1). Some complementary therapies are passive (eg, background music, massage therapy, acupuncture), while others require active patient

TABLE 1 Definition of Modalities

Modality	Definition
Massage therapy	Group of systematic and scientific manipulations of body tissues best performed with the hands to affect the nervous and muscular systems and general circulation.
Mind-body, other relaxation techniques	Methods that emphasize mind-body interactions with intended benefits that include relaxation and emotional well-being.
Music therapy	The use of music to help treat neurologic, mental, and behavioral disorders.
Acupuncture therapy	Treatment of symptoms involving the insertion of needles along specific pathways. Placement varies by problem. It is sometimes used in conjunction with heat, moxibustion, acupuncture, or electric stimulation.
Dietary supplements	Products in capsule, tablet, liquid, or dried form, including vitamins, proteins, herbs, and other over-the-counter substances.

participation (eg, self-hypnosis, yoga, meditation). Patient preference is an important issue, as many patients prefer passive interventions, while others seek active means of participating in their own care, and still other patients prefer both, depending on the problem they hope to address. This article deals with potentially useful complementary therapies and with herbs and other botanicals. Discussion of complementary therapies for mood disorders such as depression and anxiety follows a review of pain management; implications for clinicians conclude this review.

CANCER-RELATED PAIN

Pain experienced by cancer patients can result from diagnostic or therapeutic procedures, direct tumor involvement, long-term effects of treatment, or unrelated benign conditions. Pain can be nociceptive or neuropathic. The latter is often more difficult to treat. Some cancer patients have a combination of the two types of pain.²⁻⁴

National Comprehensive Cancer Network guidelines recommend consideration of non-pharmacologic modalities such as massage, acupuncture, imagery/hypnosis, and relaxation training if pain scores remain 4 or above on a 10-point scale following reevaluation and modification of pharmacologic management.⁵ In the absence of specific guidelines concerning when and how to incorporate complementary therapies, such decisions typically are based on clinical judgment and patient preference. Risk/benefit ratio is an additional useful guideline.

Procedural Pain

Complementary therapies can lessen procedural pain. Fear, anxiety, and tension heighten pain perception, more so in procedural than in chronic pain. Although this is especially noticeable in pediatric patients, even adult patients may be fearful and uncomfortable with the sense of lack of control. This may result in poor cooperation during procedures, leading to usually unnecessary amounts of analgesics and sedatives. Complementary modalities before and during procedures can help reduce these problems.

Complementary therapies have been studied in clinical trials for pain and distress associated with lumbar puncture, catheter placement, bone marrow aspiration, endoscopy, and skin and breast biopsy. Most studies show beneficial effects.⁶⁻⁸ For example, 30 pediatric patients undergoing bone marrow aspiration were randomized to hypnosis, a package of cognitive behavioral coping skills, or no intervention. Those who received either hypnosis or cognitive behavioral therapy experienced more pain relief than control patients. The effects were similar between hypnosis and cognitive behavioral therapy. Both therapies also reduced anxiety and distress, with hypnosis showing greater effectiveness.⁹

Patients can be taught mind-body techniques such as self-hypnosis, guided imagery, and relaxation techniques to use before and during painful or stressful procedures, chemotherapy, or radiation therapy. Patients typically learn these techniques quickly. After a few sessions, they can continue to self-

treat, making these techniques convenient and cost effective and providing them with a degree of control. Patients with substantial anxiety or fear about pending procedures or who need an enhanced sense of control should be considered for these interventions. Given available resources, mind-body techniques can be taught to pediatric cancer patients requiring repeated invasive procedures, such as bone marrow aspiration. General anxiety, which is common among cancer patients, also may be relieved with these procedures; here patient preference and risk/benefit ratio are paramount considerations.

The benefit of music therapy for procedural pain is only recently a subject of methodologically sound study, and results are equivocal. In one investigation, some patients preferred to concentrate on the medical procedure rather than on the music.¹⁰

Pain Due to Direct Tumor Involvement

Most cancer pain comes from the invasion of tissue by tumor or its pressure on nerves. Identification and treatment of the underlying lesion is imperative for both pain control and to prevent further damage. For example, epidural metastases with impending spinal cord compression require treatment with steroids, radiation, chemotherapy, or neurosurgery. Abdominal pain due to obstruction of hollow organs requires evaluation for surgical intervention. Meanwhile, analgesics should be administered. In the acute setting, complementary therapies alone do not provide adequate pain control and are impractical, as using them typically requires multiple evaluations and interventions over a short period of time.

After the acute phase of pain management, emphasis shifts to sustaining pain relief, controlling symptoms to minimize side effects, and to psychosocial issues. The negative impact of side effects can increase with chronicity. For example, chronic constipation caused by opioids may lead to laxative abuse, causing further difficulty with bowel management. Chronic nonsteroidal anti-inflammatory drug use is associated with increased risk of gastrointestinal bleeding. Both chronic pain and chronic opioid use are associated with depression. Some

patients develop a tolerance to opioids, requiring high dosages and frequent drug rotation. For patients with difficult-to-control chronic pain, complementary therapies should be considered. Although randomized trial data are not yet reported on this issue, it is reasonable to suggest that complementary interventions can reduce the level of analgesics required by some patients, hence reducing risks associated with chronic opioid or nonsteroidal anti-inflammatory drug use. Given the cognitive/emotional sequelae of substantial opioid use, it is likely that these patients would benefit primarily from passive complementary interventions, such as massage therapy.¹¹

Mind-body techniques can be particularly useful for patients who prefer active involvement and participation. Relaxation and imagery training can reduce pain and analgesic use, thus reducing analgesic side effects in some patients.^{12,13} Hypnosis for cancer-related pain is supported by a systematic review¹⁴ and was found to be effective for mucositis pain in a randomized, controlled trial.¹⁵ Neuropathic pain usually does not respond to analgesics alone. Even with adjunct medications, many patients continue to experience this type of pain. Surgical interventions are invasive and associated with complications. In these patients, mind-body techniques may be especially worthwhile, as they may alter the perception of pain.

Pain tends to become laced with anxiety and depression in patients faced with months or years of chronic pain, and these problems can affect caregivers as well as patients. Because some complementary therapies can reduce mood disturbance as well as physical symptoms, as discussed elsewhere in this article, they can improve quality of life in general.

Massage therapy or reflexology (foot massage) may be beneficial for patients with chronic cancer pain and is increasingly available in hospital programs. Reduction of pain and anxiety has been demonstrated in randomized, controlled trials¹⁶ and also has been shown in the largest cancer data set reported.¹¹ This intervention is safe when given by properly trained massage therapists (Memorial Sloan-Kettering Cancer Center offers a course for certified massage, teaching safe and

effective practice with cancer patients). Most patients feel better after massage therapy, and it may also result in substantial relief. Receipt of massage therapy is dependent on availability and economic factors.

Acupuncture is widely used for noncancer pain. It relieves both acute pain, such as postoperative dental pain, and chronic pain, such as headache.^{17,18} Whether acupuncture relieves musculoskeletal pain is controversial,¹⁹ although it was shown to influence the production of endogenous opioid neurotransmitters.²⁰ Several single-arm studies found reduction of cancer pain, although lack of controls limited their conclusions.^{21–23}

A recent randomized, single-blinded, placebo-controlled trial tested auricular acupuncture for cancer patients who still experienced pain despite stable analgesic treatment. Ninety patients were randomized to one of three groups—needles placed at correct acupuncture points (treatment group), needles placed at non-acupuncture points, or application of pressure at nonacupuncture points (control groups). Pain intensity decreased by 36% at 2 months from baseline in the treatment group, a significant difference compared with the two control groups, where little pain reduction was seen.²⁴ These results are especially important because many patients in this trial had neuropathic pain that was refractory to conventional treatment.

Acupuncture needles are filiform, sterile, single-use needles that are thinner than insulin needles. Insertion of acupuncture needles causes minimal or no pain and much less tissue injury than phlebotomy or parenteral injection. Many patients find acupuncture treatment relaxing. However, even with the practice of aseptic technique, it is prudent not to give acupuncture to patients with neutropenia, thrombocytopenia, or risk of endocarditis due to heart valve abnormality. The current expense and inconvenience of frequent visits to acupuncturists are the most common barriers to acupuncture treatment.

Pain as a Sequela of Cancer Treatment

Chemotherapy, radiation therapy, and surgery may have long-term sequelae, including posttreatment neuropathic pain syndromes that

are difficult to manage. In the authors' clinical experience, acupuncture appears to ameliorate persistent neuropathic pain associated with thoracotomy, mastectomy, and radical neck dissection.

Chemotherapeutic drugs such as taxanes or platinum agents can cause peripheral neuropathy for which there is no reliable treatment. Dietary supplements vitamin E, alpha-lipoic acid, and glutamine showed promise in preliminary trials.^{25–27} Mind-body techniques and massage have been studied only outside of oncology, where trials of diabetic neuropathy, carpal tunnel syndrome, and human immunodeficiency virus-related neuropathy found mixed results.^{28–31}

ANXIETY AND OTHER MOOD DISTURBANCES

Cancer and its treatment typically evoke distress and emotional anguish. Patients experience fear of death, pain, disfigurement, disability, disruption of relationships, and many other distressing feelings. Depression is highly prevalent in cancer patients, where it is often underdiagnosed.^{32,33} Pharmacologic interventions such as anxiolytics and antidepressants are effective in ameliorating these symptoms, although side effects or suboptimal relief are experienced by some patients. Complementary therapies may be used as low cost, convenient adjuncts to pharmacologic agents.

Mind-body interventions, acupuncture, massage therapy, and music therapy have been studied as treatments for mood disturbance. Relaxation techniques, guided imagery, and meditation were investigated in several randomized, controlled trials and improved anxiety, depression, and other symptoms of distress.^{34–36} In one study, improvements were maintained at 6-month follow-up.³⁷ Acupuncture may reduce preoperative anxiety,³⁸ but there is no report of its direct effects on general anxiety in cancer patients. Two single-arm pilot studies of acupuncture showed decreased mood disturbance associated with hormonal treatment in breast and prostate cancer patients.^{39,40} Controlled trials show that massage therapy also can enhance mood.^{41–43} Music therapy is a noninvasive and inexpensive intervention that appears to reduce

mood disturbance in patients experiencing the stress of pending bone marrow transplantation.⁴⁴

Given the current level of evidence and the risk/benefit factor, complementary modalities should be considered for appropriate patients. Patients with mood disturbance require evaluation first to uncover any problems requiring immediate psychiatric referral, such as panic attack or suicidal ideation, before complementary therapies are considered. Patients who do not require immediate intervention can be further stratified. Those with recent onset of symptoms may be candidates for complementary therapies, as they are likely to be diagnosed with adjustment disorder. For them, anxiolytics may bring unnecessary side effects. Antidepressants require weeks to show an effect. Mind-body techniques in particular can help these patients cope with distressful situations, such as learning the news of cancer diagnosis or recurrence. In addition, complementary therapies avoid the stigma that patients sometimes associate with psychotherapy and psychotropic medications, and they (with the exception of certain dietary supplements) are quite safe.

For patients with long-standing symptoms and established diagnoses of general anxiety or major depression, pharmacologic interventions remain the most effective measures. Even with these patients, however, discussion will identify those who desire and could benefit from complementary therapies. Complementary modalities may

reduce the amount of medication needed. They also empower patients to gain some control over their well-being and provide a sense of participation in the healing process. Many cancer patients use complementary and alternative medicine (CAM) therapies on their own; it is clinically important that their physicians and other health professionals guide patients away from bogus therapies and toward appropriate complementary interventions.

Some patients use herbs and dietary supplements for relief of anxiety, depression, and physical symptoms. These products are readily available as dietary supplements. Indeed, many botanicals contain biologically active substances that can effectively change mood or relieve pain. However, herbs and other botanical products should not be used during chemotherapy, radiation, or when surgery is planned, as they can interfere with prescription medications, alter coagulation, modulate the level and activity of drug-metabolizing enzymes, and produce herb-drug interactions.⁴⁵ For example, St. John's Wort treats mild and moderate depression⁴⁶⁻⁴⁸ but adversely impacts the efficacy of some chemotherapy and other prescription medications.⁴⁹⁻⁵⁴ Table 2 lists botanicals that patients often use for mood disturbance and indicates their biologic activities and potential adverse effects.

Some studies of dietary supplements for mood disturbance have been conducted. s-Adenosylmethionine was found to have an antidepressant

TABLE 2 Common Herbs Used for Mood Disturbance*

Name	Used For	Known Effects	Adverse Reactions
Kava Kava	Anxiety	Anxiolytic	Additive effects with central nervous system depressants, hepatotoxicity
Ephedra (Mahuang) Valerian	Asthma, stimulant, appetite suppressant Sleep aid	Adrenergic agonist Appears to be mediated through gamma-aminobutyric acid and benzodiazepine pathway	Heart attack, seizure, psychosis Additive effects with barbiturates and benzodiazepines, withdrawal syndrome
St. John's Wort	Depression, seasonal affective disorder, and anxiety ⁵⁵	Inhibits the reuptake of serotonin, dopamine, norepinephrine, gamma-aminobutyric acid, and L-glutamine in vitro	Interacts with the drug metabolizing enzyme CYP 3A4, lowers efficacy of irinotecan and tamoxifen, among others
Passionflower	Insomnia, anxiety, epilepsy, neuralgia, and opiate or benzodiazepine withdrawal	May cause activation of gamma-aminobutyric acid receptors	May potentiate the sedative effect of centrally acting substance
Ginkgo biloba	Dementia, peripheral vascular disorders, sexual dysfunction, and hearing loss	Improves cognition, activities of daily living, and mood and emotional function	A few case reports of spontaneous bleeding and seizures

*Not recommended for cancer patients.

effect comparable with that of standard tricyclics.⁵⁶ It may induce mania in bipolar patients. Phenylalanine enhances the effects of monoamine oxidase inhibitors.⁵⁷ Omega-3 polyunsaturated fatty acids, particularly docosahexaenoic acid, may have mood-stabilizing effects.⁵⁸ Low folate level was associated with poorer response to fluoxetine.⁵⁹ Despite these benefits, dietary supplements are highly problematic in cancer patients. Patients often harbor the misconception that because dietary supplements are natural, they are always safe and free of side effects. This is far from accurate. Lack of product standardization and inadequate quality control during manufacturing and packaging are significant problems. The constituents and amount of active ingredient, if known, vary considerably by manufacturer and batch. The inconsistency and complexity of these products may produce unpredictable adverse effects or interactions with prescription medications.

Tryptophan, for example, used to enhance the effects of antidepressants,⁶⁰ is no longer marketed in the United States after contaminated tryptophan was associated with eosinophilia-myalgia syndrome.⁶¹ St. John's Wort can induce the expression of the cytochrome P450 CYP3A4 isoform, an enzyme involved in drug metabolism. When St. John's Wort and irinotecan are coadministered, the serum level of an active metabolite of irinotecan is lowered, indicating detrimental impact on cancer treatment efficacy.⁴⁹ Patients should be educated about the problems of taking botanical supplements while under cancer treatment or with any prescription medication.⁶² Memorial Sloan-Kettering Cancer Center regulations preclude their use during active cancer treatment.

IMPLICATIONS FOR CLINICIANS

Complementary therapies are helpful for some but not all patients. Parameters that identify "good responders" are lacking. Complementary therapies such as mind-body techniques and mas-

sage therapies are safe assuming they are provided by licensed, competent practitioners such as those employed in many cancer programs throughout North America. Acupuncture is associated with minimal risk. With the notable exception of herb-drug interactions associated with certain dietary supplements, no complementary modality is, in our experience, associated with the frequency and severity of risk attached, for example, to mainstream cancer therapies or to most prescription medications. Although 57% to more than 80% of cancer patients use one or more CAM interventions,⁶³ not all patients have access to the full range of CAM, as these therapies rarely are covered by insurance. This is unfortunate because patients with intractable symptoms are among the heaviest users of health care services, and beneficial complementary therapies can relieve symptoms, promote self-care, and decrease health care costs.

As reviewed here, research suggests that complementary measures are useful under many circumstances. Because strong evidence concerning measurable benefit for specific indications is not always available, clinical decisions should be based on the balance of evidence concerning efficacy and safety,⁶⁴ on the risk/benefit ratio, and on patient preference. These three factors—research evidence, clinical judgment and risk/benefit assessment, and patient preference—will successfully guide practitioners to make appropriate recommendations.

Herbs and other dietary supplements used in conjunction with prescription medication may be dangerous because of potential herb-drug interactions.⁴⁵ However, the judicious integration of touch therapies, mind-body therapies, acupuncture, and other complementary therapies into cancer patient care is warranted. Given patient interest, these therapies are likely to reduce troubling physical and emotional symptoms, offer patients a measure of control over their well-being, enhance quality of life, and improve both patient satisfaction and the physician-patient relationship.

REFERENCES

1. Vickers AJ, Cassileth BR. Unconventional therapies for cancer and cancer-related symptoms. *Lancet Oncol* 2001;2:226–232.
2. Curtis EB, Krech R, Walsh TD. Common symptoms in patients with advanced cancer. *J Palliat Care* 1991;7:25–29.
3. Donnelly S, Walsh D. The symptoms of advanced cancer. *Semin Oncol* 1995;22(2)

Suppl 3):67-72.

4. Chang VT, Hwang SS, Feuerman M, Kasimis BS. Symptom and quality of life survey of medical oncology patients at a veterans affairs medical center: a role for symptom assessment. *Cancer* 2000;88:1175-1183.
5. Benedetti C, Brock C, Cleeland C, et al. NCCN practice guidelines for cancer pain. *Oncology (Huntingt)* 2000;14:135-150.
6. Kazak AE, Penati B, Brophy P, Himelstein B. Pharmacologic and psychologic interventions for procedural pain. *Pediatrics* 1998;102:59-66.
7. Montgomery GH, Weltz CR, Seltz M, Bovbjerg DH. Brief presurgery hypnosis reduces distress and pain in excisional breast biopsy patients. *Int J Clin Exp Hypn* 2002;50:17-32.
8. Zeltzer L, LeBaron S. Hypnosis and nonhypnotic techniques for reduction of pain and anxiety during painful procedures in children and adolescents with cancer. *J Pediatr* 1982;101:1032-1035.
9. Lioffi C, Hatira P. Clinical hypnosis versus cognitive behavioral training for pain management with pediatric cancer patients undergoing bone marrow aspirations. *Int J Clin Exp Hypn* 1999;47:104-116.
10. Kwekkeboom KL. Music versus distraction for procedural pain and anxiety in patients with cancer. *Oncol Nurs Forum* 2003;30:433-440.
11. Cassileth BR, Vickers AJ. Massage therapy for symptom control: outcome study at a major cancer center. *J Pain Symptom Manage* 2004;28:244-249.
12. Sloman R, Brown P, Aldana E, Chee E. The use of relaxation for the promotion of comfort and pain relief in persons with advanced cancer. *Contemp Nurse* 1994;3:6-12.
13. Syrjala KL, Donaldson GW, Davis MW, et al. Relaxation and imagery and cognitive-behavioral training reduce pain during cancer treatment: a controlled clinical trial. *Pain* 1995;63:189-198.
14. Sellick SM, Zaza C. Critical review of 5 nonpharmacologic strategies for managing cancer pain. *Cancer Prev Control* 1998;2:7-14.
15. Syrjala KL, Cummings C, Donaldson GW. Hypnosis or cognitive behavioral training for the reduction of pain and nausea during cancer treatment: a controlled clinical trial. *Pain* 1992;48:137-146.
16. Wilkie DA, Kampbell J, Cutshall S, et al. Effects of massage on pain intensity, analgesics and quality of life in patients with cancer pain: a pilot study of a randomized clinical trial conducted within hospice care delivery. *Hosp J* 2000;15:31-53.
17. NIH Consensus Conference. Acupuncture. *JAMA* 1998;280:1518-1524.
18. Melchart D, Linde K, Fischer P, et al. Acupuncture for recurrent headaches: a systematic review of randomized controlled trials. *Cephalalgia* 1999;19:779-786.
19. Ernst E, Pittler MH. The effectiveness of acupuncture in treating acute dental pain: a systematic review. *Br Dent J* 1998;184:443-447.
20. Guo HF, Tian J, Wang X, et al. Brain substrates activated by electroacupuncture of different frequencies (I): comparative study on the expression of oncogene c-fos and genes coding for three opioid peptides. *Brain Res Mol Brain Res* 1996;43:157-166.
21. Filshie J, Redman D. Acupuncture and malignant pain problems. *Eur J Surg Oncol* 1985;11:389-394.
22. Leng G. A year of acupuncture in palliative care. *Palliat Med* 1999;13:163-164.
23. Alimi D, Rubino C, Leandri EP, Brule SF. Analgesic effects of auricular acupuncture for cancer pain. *J Pain Symptom Manage* 2000;19:81-82.
24. Alimi D, Rubino C, Pichard-Leandri E, et al. Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial. *J Clin Oncol* 2003;21:4120-4126.
25. Pace A, Savarese A, Picardo M, et al. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol* 2003;21:927-931.
26. Gedlicka C, Kornek GV, Schmid K, Scheithauer W. Amelioration of docetaxel/cisplatin induced polyneuropathy by alpha-lipoic acid. *Ann Oncol* 2003;14:339-340.
27. Vahdat L, Papadopoulos K, Lange D, et al. Reduction of paclitaxel-induced peripheral neuropathy with glutamine. *Clin Cancer Res* 2001;7:1192-1197.
28. Hamza MA, White PF, Craig WF, et al. Percutaneous electrical nerve stimulation: a novel analgesic therapy for diabetic neuropathic pain. *Diabetes Care* 2000;23:365-370.
29. Garfinkel MS, Singhal A, Katz WA, et al. Yoga-based intervention for carpal tunnel syndrome: a randomized trial. *JAMA* 1998;280:1601-1603.
30. Shlay JC, Chaloner K, Max MB, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. *JAMA* 1998;280:1590-1595.
31. Abuaisa BB, Costanzi JB, Boulton AJ. Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study. *Diabetes Res Clin Pract* 1998;39:115-121.
32. Holland JC. Preliminary guidelines for the treatment of distress. *Oncology (Huntingt)* 1997;11:109-114.
33. Spiegel D, Giese-Davis J. Depression and cancer: mechanisms and disease progression. *Biol Psychiatry* 2003;54:269-282.
34. Petersen RW, Quinlivan JA. Preventing anxiety and depression in gynaecological cancer: a randomised controlled trial. *Br J Obstet Gynaecol* 2002;109:386-394.
35. Specia M, Carlson LE, Goodey E, Angen M. A randomized, wait-list controlled clinical trial: the effect of a mindfulness meditation-based stress reduction program on mood and symptoms of stress in cancer outpatients. *Psychosom Med* 2000;62:613-622.
36. Targ EF, Levine EG. The efficacy of a mind-body-spirit group for women with breast cancer: a randomized controlled trial. *Gen Hosp Psychiatry* 2002;24:238-248.
37. Carlson LE, Ursuliak Z, Goodey E, et al. The effects of a mindfulness meditation-based stress reduction program on mood and symptoms of stress in cancer outpatients: 6-month follow-up. *Support Care Cancer* 2001;9:112-123.
38. Wang SM, Peloquin C, Kain ZN. The use of auricular acupuncture to reduce preoperative anxiety. *Anesth Analg* 2001;93:1178-1180.
39. Porzio G, Trapasso T, Martelli S, et al. Acupuncture in the treatment of menopause-related symptoms in women taking tamoxifen. *Tumori* 2002;88:128-130.
40. Hammar M, Frisk J, Grimas O, et al. Acupuncture treatment of vasomotor symptoms in men with prostatic carcinoma: a pilot study. *J Urol* 1999;161:853-856.
41. Ahles TA, Tope DM, Pinkson B, et al. Massage therapy for patients undergoing autologous bone marrow transplantation. *J Pain Symptom Manage* 1999;18:157-163.
42. Stephenson NL, Weinrich SP, Tavakoli AS. The effects of foot reflexology on anxiety and pain in patients with breast and lung cancer. *Oncol Nurs Forum* 2000;27:67-72.
43. Smith MC, Kemp J, Hemphill L, Vojir CP. Outcomes of therapeutic massage for hospitalized cancer patients. *J Nurs Scholarsh* 2002;34:257-262.
44. Cassileth BR, Vickers AJ, Magill LA. Music therapy for mood disturbance during hospitalization for autologous stem cell transplantation: a randomized controlled trial. *Cancer* 2003;98:2723-2729.
45. Memorial Sloan-Kettering Cancer Center. Information resource: about herbs, botanicals, and other products. Available at: www.mskcc.org/mskcc/html/11570.cfm. Accessed November 10, 2004.
46. Hypericum Depression Trial Study Group. Effect of Hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial. *JAMA* 2002;287:1807-1814.
47. Woelk H. Comparison of St John's wort and imipramine for treating depression: randomised controlled trial. *Br Med J* 2000;321:536-539.
48. Lecrubier Y, Clerc G, Didi R, Kieser M. Efficacy of St. John's wort extract WS 5570 in major depression: a double-blind, placebo-controlled trial. *Am J Psychiatry* 2002;159:1361-1366.
49. Mathijssen RH, Verweij J, de Bruijn P, et al. Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002;94:1247-1249.
50. Burstein AH, Horton RL, Dunn T, et al. Lack of effect of St John's Wort on carbamazepine pharmacokinetics in healthy volunteers. *Clin Pharmacol Ther* 2000;68:605-612.
51. de Maat MM, Hoetelmans RM, Math RA, et al. Drug interaction between St John's wort and nevirapine. *AIDS* 2001;15:420-421.
52. Durr D, Stieger B, Kullak-Ublick GA, et al. St John's Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clin Pharmacol Ther* 2000;68:598-604.
53. John A, Brockmoller J, Bauer S, et al. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). *Clin Pharmacol Ther* 1999;66:338-345.
54. Moore LB, Goodwin B, Jones SA, et al. St.

- John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. *Proc Natl Acad Sci USA* 2000;97:7500–7502.
55. Schrader E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. *Int Clin Psychopharmacol* 2000;15:61–68.
56. Bressa GM. S-adenosyl-l-methionine (SAME) as antidepressant: meta-analysis of clinical studies. *Acta Neurol Scand Suppl* 1994;154:7–14.
57. Sabelli HC, Javaid JI. Phenylethylamine modulation of affect: therapeutic and diagnostic implications. *J Neuropsychiatry Clin Neurosci* 1995;7:6–14.
58. Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56:407–412.
59. Fava M, Borus JS, Alpert JE, et al. Folate, vitamin B12, and homocysteine in major depressive disorder. *Am J Psychiatry* 1997;154:426–428.
60. Walinder J, Skott A, Carlsson A, et al. Potentiation of the antidepressant action of clomipramine by tryptophan. *Arch Gen Psychiatry* 1976;33:1384–1389.
61. Hertzman PA, Blevins WL, Mayer J, et al. Association of the eosinophilia-myalgia syndrome with the ingestion of tryptophan. *N Engl J Med* 1990;322:869–873.
62. Beaubrun G, Gray GE. A review of herbal medicines for psychiatric disorders. *Psychiatr Serv* 2000;51:1130–1134.
63. Vashi PG, Lammersfeld CA, Grutsch T, et al. Complementary and alternative medicine (CAM) use among cancer patients: prevalence, patterns, and perceived benefit prior to admission [abstract]. *Proc Am Soc Clin Oncol* 2003; 22:560.
64. Weiger WA, Smith M, Boon H, et al. Advising patients who seek complementary and alternative medical therapies for cancer. *Ann Intern Med* 2002;137:889–903.